CORONAVIRUS VACCINES

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Review

- Coronavirus Pathogenesis
- Coronavirus Vaccines
- Lessons from the Past
- Recommendations

Pathogenesis-

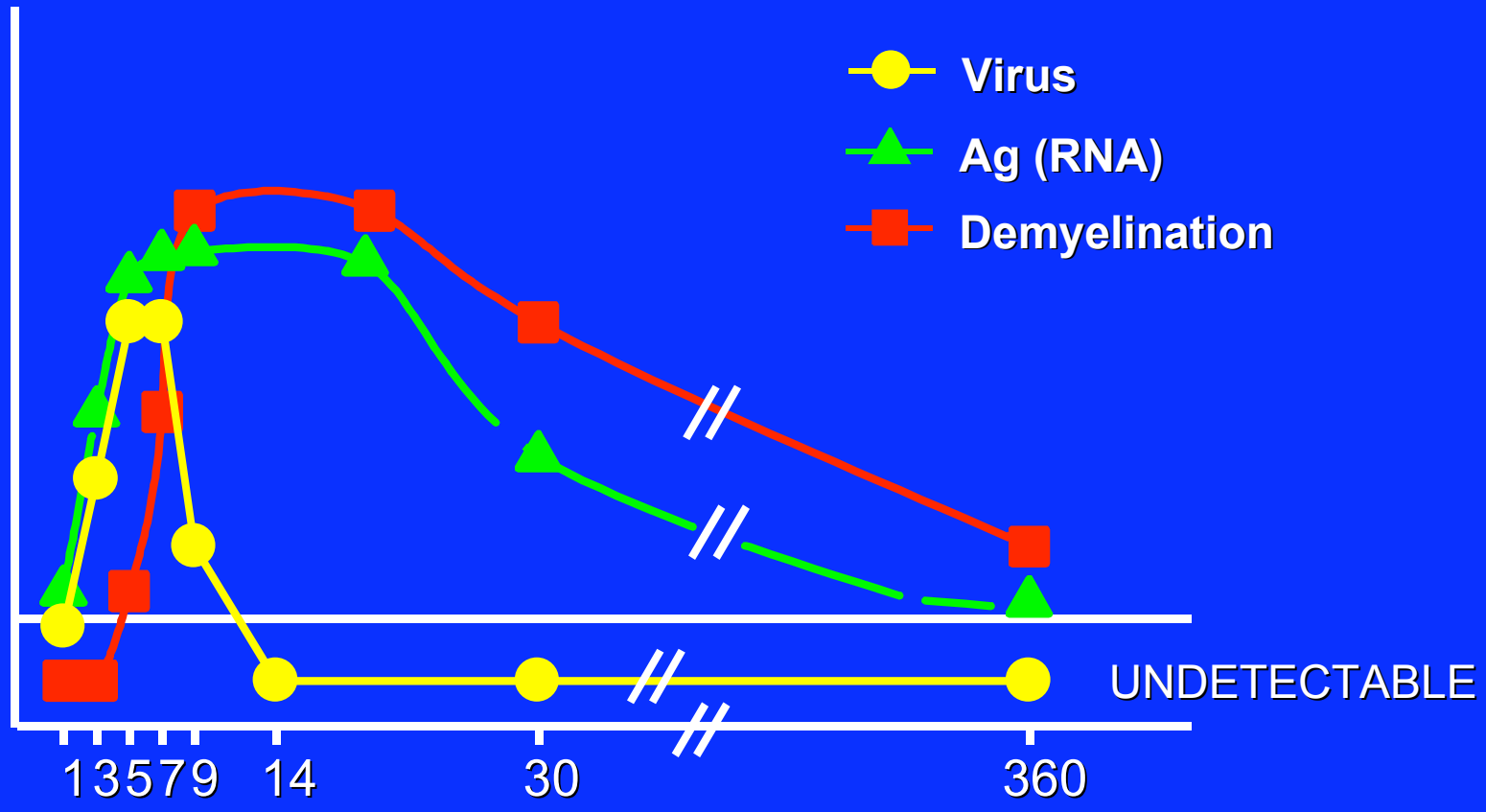
Mechanism by which a pathogen causes a disease

Understand pathogenesis, design rational approaches for abrogating disease processes, identify components of protective immunity

Develop effective vaccines

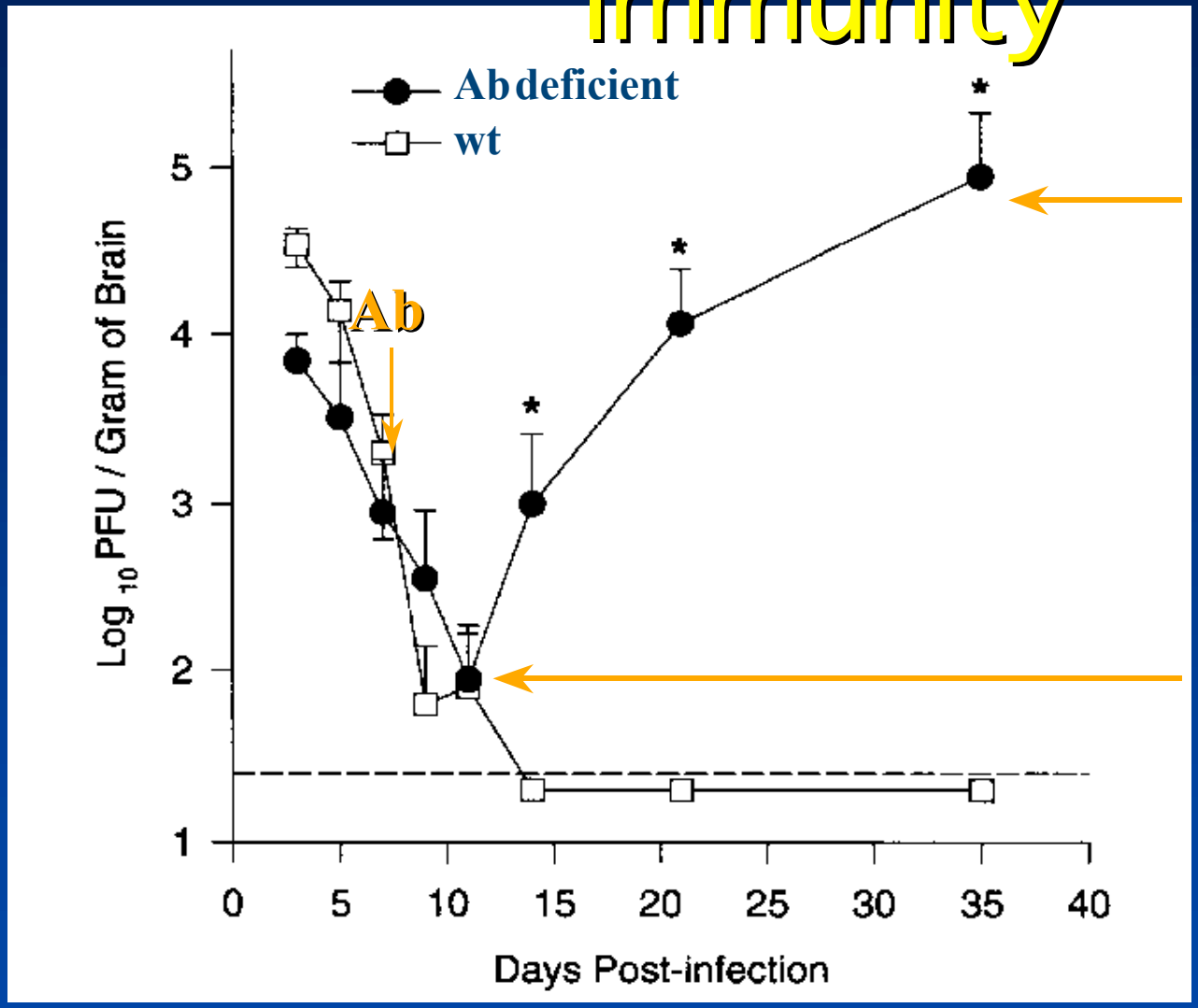
Stohlman and Bergmann

PATHOGENESIS OF JHM VIRUS IN MICE



*Is SARS pathogenesis virus-induced or immue mediated? How long will it persist? Where will it persist? What is responsible for virus clearance?

Components of Protective Immunity



Virus reactivation

Incomplete viral clearance

Lin et. al., JImmunol162:7358, 1999 Ramakrishna et al., JImmunol168:1204, 2002

*Both cellular and humoral immunity are required for virus clearance.

CORONAVIRUS PATHOGENESIS

	Coronavirus				
Infected	Macaque	PIGS		Cattle	
Tissues	SARS	TGEV-V	PRCV	BCoV-E	BCoV-R
Viremia	+/-	-	+	ND	ND
Upper Resp. Tract	+	+	++	+	++
Lower Resp. Tract	++	+/-	+++	+	+++
Intestine	+/-	+++	+/-	++ (colon)	++ (colon)

SARS is likely a pneumoenteric pathogen, like TGEV, PRCV, BCoV-E and BCoV-R (Mucosal Immunity is likely critical for protection).

PROTECTIVE IMMUNITY

- Balanced cellular and humoral immune responses, likely to multiple structural and nonstructural proteins
- As many coronaviruses cause pneumoenteric infections, mucosal immunity should be targeted to both compartments
  - Pneumoenteric viruses, mucosal protection in the lungs does not protect against enteric disease and shedding
- Viremia to traffic between compartments? Macrophage Infecction?
- Concern: low level immunity (BoCV-R), short-lived mucosal immunity and Antibody Dependent Enhancement (FIPV)

Vaccines

- Reinfection is common although clinical disease is usually reduced upon second exposure
- Persistence with shedding is also common

Coronavirus Vaccine Challenges

- Human coronavirus infection elicits short-lived immunity and individuals can be successfully infected ~2yrs postchallenge. Human coronavirus sequence persists in the CNS. *SARS?*
- Live-attenuated, inactivated and subunit based vaccines not only failed to protect, but resulted in antibody mediated immune enhancement of FIPV infection with increased disease and death
  - antibody against S glycoprotein

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- Live-attenuated, inactivated and subunit based vaccines not only failed to protect, but resulted in immune enhancement of FIPV infection and disease
  - neutralizing antibody against S glycoprotein
- Inactivated vaccines and recombinant proteins did not protect against TGEV, BoCV, FIPV and CCoV infection
- Live-attenuated IBV (very protective) and TGEV vaccines are somewhat efficacious. Live-attenuated BCV protects against clinical disease but not infection (IBV vaccines: little protection from heterologous strains; may be short term immunity).
- Vectored vaccines (Adenovirus/poxviruses) provided limited protection against TGEV, more efficacious against IBV

Coronavirus Vaccines

- In the case of TGEV and BCoV, goal of vaccine is to induce the passive transfer of protective lactogenic immunity to the newborn (clearly different than SARS)

- Except IBV (goal is short term immunity) and TGEV live attenuated vaccines, a coronavirus vaccine that prevents both respiratory and enteric disease has been difficult to produce.

- Immune Targets: S glycoprotein, N protein, other structural proteins, replicase?

Lessons from the Past

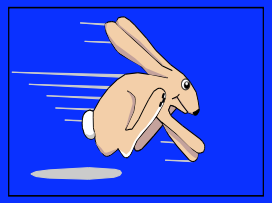
- What might the future hold for SARS?
- Can SARS change its transmission and clinical presentation?
- Is SARS an anomaly or a harbinger of the emerging potential of coronaviruses and other members of the Nidovirus Order?

Lessons from the Past

Nidovirus Pandemics Since 1978

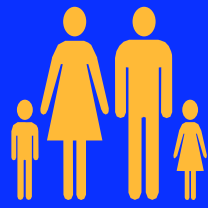
- **1978:** Porcine epidemic diarrhea virus (PEDV) emerged in Belgium and the UK . The most important viral infection of the swine intestinal track in Europe and Asian Nations
  - I. profuse watery diarrhea with high mortality (50% in <4-5 week animals; II. All ages but less severe in adults [3%])
  - Sequence more akin to HCV 229E
- **1984**: Porcine Respiratory Coronavirus (PRCoV) evolved from TGEV (enteric) pathogen.
  - Single amino acid change or a deletion (in S1 regulates enteric or respiratory tropism (Also removes two antigenic sites)
  - Worldwide distribution, PRCV cross protection against TGEV, TGEV prevalence is declining in Europe

Paradigm for many New Emerging Viruses



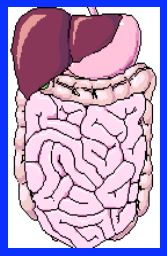
SARS

PEDV

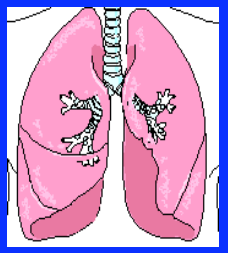


Animal Reservoir

Humans



Tropism Change



Lessons from the Past
Nidovirus Pandemics/ Emerging Pathogens

- 1987-90: Porcine Respiratory and Respiratory Disease Syndrome (PRRSV) emerged simultaneously in the US and Europe (Origin is unknown)
  - Germany 1990-All of Europe by 1991
  - Most important swine pathogen (pneumonia and fetal loss)
- 1993: Respiratory Bovine Coronavirus-"Shipping Fever" Pneumonia
  - Changes in pol1a and S glycoprotein gene (single change) likely responsible for change in tropism/virulence from enteric (BoCV-E) to respiratory disease (BCoV-R)
- SARS Pandemic? Origin of the SARS virus is likely a zoonosis from civit cats; ~15% mortality, >50% in elderly populations
- **Common Theme**:
  - In each case, losses continue despite widespread use of modern management and vaccination programs (**Time: we need to prepare quickly; He's is a nasty guy**)

Recommendations

CORONAVIRUS PATHOGENESIS

- SARS Pathogenesis in Humans
- Develop SARS Animal Models (e.g., facilities, standardized reagents, biological specimens, communication)
  - Identify Sites of Replication, Target Cell Populations, Pathogenic Mechanisms, Mechanisms of Spread and Persistence
  - Identify Components of Innate and Protective Immunity
  - Identify Virulence Determinants (e.g., S hypervariable regions, IFN antagonists, Antibody Dependent Enhancement)
  - Pathogenesis Studies and Test Candidate Vaccines

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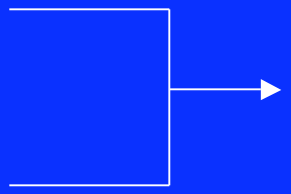
  - Test Candidate Vaccines
- Support Large and Small Animal Models of Coronavirus Pathogenesis (e.g., MHV and BCoV-R)
- Sample the Biodiversity of Coronaviruses
  - SARS Related Isolates (e.g., Civit Cat, Raccoon Dog)
  - Other Unrecognized Coronaviruses (e.g., consensus PCR, Array Screening, Serology) Sequence these isolates, develop a sequence database as a resource.

CORONAVIRUS VACCINES

- Develop Multiple High Throughput Candidate Vaccines
  - Live Attenuated (most success)
  - Recombinant Vectored (fast)
  - Prime-Boost Approaches
  - Inactivated/subunit vaccines (?, less likely to succeed)



- Mucosal Immunity at Enteric and Respiratory Surfaces

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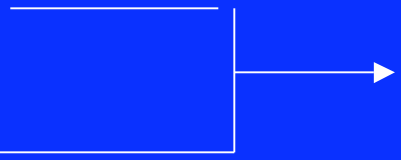

- Mucosal Immunity at Enteric and Respiratory Surfaces
- Target Multiple Immunogens
  - S glycoprotein, N protein, replicase proteins and other structural and nonstructural targets of humoral and cellular immunity
- Develop Genetic Approaches for Live Attenuated Virus Vaccine Development
  - SARS Reverse Genetics
  - SARS Targeted RNA Recombination

Vaccine Related Basic Research
(Potential for Antiviral/Vaccine Escape and Emergence)

- Model SARS/Coronavirus Evolution
  - Mutation and RNA Recombination Frequency
  - Plasticity of Structural Proteins (S glycoprotein hypervariable domain, function of group specific genes)
  - Mechanisms of Tissue Tropism Switching
  - Evolution of Immunodominant Epitopes
  - Phylogeny
- Define Coronavirus Persistence in vivo
  - Mechanisms of Coronavirus Persistence in vivo
  - Mechanisms of Coronavirus immune avoidance
- Elucidate the Cross Species Potential of Coronaviruses
- Basic Research on Model Coronaviruses